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# European Organization for Research and Treatment of Cancer (EORTC) 08957 Phase II Study of Topotecan in Combination with Cisplatin as Second-Line Treatment of Refractory and Sensitive Small Cell Lung Cancer

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## ABSTRACT

*Purpose:* The purpose of this study was to assess the activity and toxicity of a combined regimen of topotecan and cisplatin in "sensitive" (s) and "refractory" (r) small-cell lung cancer (SCLC) patients treated previously.

*Experimental Design:* Patients with measurable SCLC and progressive disease after one first-line regimen were eligible for the study. Patients were enrolled in two separate groups: r group (patients who failed first-line treatment <3 months from treatment discontinuation) and s group (patients who responded to first-line treatment and progressed ≥3 months after treatment discontinuation). Cisplatin was given i.v. at the dose of 60 mg/m$^2$ on day 1, and topotecan was administered as a daily i.v. infusion at the dose of 0.75 mg/m$^2$ from day 1 to 5, every 3 weeks.

*Results:* A total of 110 eligible (68 s and 42 r) patients were enrolled from 24 institutions. The main patient characteristics were as follows: median age 60 (s) and 55 (r) years, median performance status 1 for both (s) and (r). Seventy-four percent (s) and 67% (r) had extensive stage disease, including 22% and 36% respectively, with brain metastases. A total of 398 chemotherapy courses were administered [median 4 (s) and 3 (r) per patient]. The most frequent and serious toxicity was myelosuppression. Grade ΓV neutropenia occurred in 62% (s) and 49% (r) of patients, with a 19% (s) and 15% (r) incidence of febrile neutropenia, and grade IV thrombocytopenia in 54% (s) and 44% (r). Most of these toxicities occurred during the first chemotherapy course and led to topotecan dose reduction and/or delay in the following courses. Grade III-IV nonhematological toxicity was uncommon. Five deaths possibly related to toxicity occurred among s patients only. Objective responses have been documented in 20 s patients, 19 partial responses and 1 complete response, (29.4% response rate; 95% confidence interval, 19-42), whereas, among r patients, 10 partial responses have been observed (23.8% response rate; 95% confidence interval, 12-39). Median survival for s and r was 6.4 and 6.1 months, respectively.

*Conclusions:* The combination of cisplatin and topotecan, at this dose and schedule, shows activity and promising results in patients with refractory SCLC, with reversible myelosuppression being the main side effect. Additional development of this regimen, using better-tolerated schedules, is warranted in patients with refractory SCLC.

## INTRODUCTION

Although SCLC[3] is highly responsive to initial chemotherapy, the vast majority of patients experience tumor progression within 6-12 months after completion of first-line treatment (1). Results of second-line chemotherapy are usually poor. The most active single agents yield response rates in the range of 10-30% (2), and activity of combination chemotherapy regimens is usually <40% (3, 4). In addition, duration of response to second-line chemotherapy is short, with a median survival that rarely exceeds 6 months (5). There is no standard chemotherapy for second-line treatment of SCLC. However, for patients progressing after first line platinum-etoposide, cyclophosphamide-adriamycin-vincristine-like regimens are widely used, whereas for patients relapsing after a nonplatinum based chemotherapy, such as cyclophosphamide-adriamycin-vincristine/adriamycin-cyclophosphamide-etoposide, a cisplatin based regimen, such as platinum-etoposide, is common practice (6, 7).

To better characterize patients with relapsed SCLC, the EORTC Lung Cancer Group has identified two categories of patients based on their different probability of responding to second-line chemotherapy, r patients are those who have never responded to first-line chemotherapy or who have responded but progressed within 3 months from the end of induction treatment. s are those who have responded to first-line chemotherapy and relapsed after a treatment-free interval of ≥3 months (8). Refractory SCLC patients rarely respond to second-line single-agent chemotherapy and may only respond to true "noncross resistant" combination-chemotherapy (9), whereas sensitive patients have a reasonable chance of responding to second-line chemotherapy or even to first-line chemotherapy rechallenge (10). Among new active agents in the treatment of SCLC, camptothecin analogues have emerged as most promising, and topotecan, a semisynthetic water-soluble analogue of camptothecin with specific targeting to topoisomerase-I, has been extensively tested in the second-line therapy of SCLC. A Phase II single agent study conducted within our group, along with a number of other prospective trials, has documented activity in both r and s disease with a response rate ranging from 2 to 11% and from 14 to 38%, respectively (11-15). On the basis of the results of our previous single agent topotecan study, we conducted two parallel Phase II studies, one in patients with r and the other in patients with s SCLC, aiming at assessing the antitumor activity and toxicity of a combination regimen including topotecan and cisplatin (16).

## PATIENTS AND METHODS

**Eligibility.** Eligible patients were required to meet all of the following criteria: histologically confirmed diagnosis of SCLC, presence of at least one bidimensionally measurable target lesion outside areas of prior radiotherapy, age 18-75 years inclusive, WHO performance status ≤2, and evidence of progressive disease after one first-line chemotherapy not including camptothecin analogues. Prior chemotherapy with cisplatin was permitted only in case of response and if chemotherapy treatment had been completed at least 6 months before. Patients treated twice with the same first-line chemotherapy regimen were also considered eligible. Patients must have stopped all of the previous chemotherapy and radiotherapy at least 4 weeks before study entry, and must have recovered from the side effects of any prior therapy. Patients with asymptomatic brain metastases were eligible. In the patients who had not received prior cranial irradiation (either as prophylaxis or as treatment), palliative brain radiotherapy was allowed at the end of topotecan treatment or concurrently, if brain lesions were not used as indicator lesions. Patients with symptomatic brain metastases were eligible only if adequately treated with prior standard radiotherapy and steroids. At entry, eligible patients were required to have adequate hematological, renal, and hepatic functions as defined by ANC ≥1.5 x $10^9$/liter, platelet count >100 x $10^9$/liter, hemoglobin >9 g/dl, total bilirubin ≤1.25 times the upper normal limit, serum creatinine within the normal range, and a calculated creatinine clearance >60 ml/min. Patients with increased total bilirubin (up to 2.5 times the upper normal limit) because of liver metastases were also considered eligible. Written informed consent had to be obtained from all of the patients, and documented according to national regulatory requirements and to the local institution rules. However, in the course of the trial, the informed consent could not be documented during monitoring on site for 14 patients included in the trial. Although we could not retrieve the documentation of the informed consent, 13 of these patients were checked on all of the other source data. For 1 patient, the medical file could not be retrieved. For all of these patients, the responsible investigator has stated that he/she fully informed the patient orally on all aspects of the trial and certifies that each patient agreed to participate in the trial.

Patients with pre-existing, uncontrolled cardiac disease, documented myocardial infarction in the prior 3 months, motor or sensory neuropathy ≥grade II, active infection, past or current history of neoplasms except for curatively treated nonmelanoma skin cancer or carcinoma *in situ* of the cervix were excluded from this study. The study was approved by the EORTC Protocol Review Committee and by the ethics committees of the participating centers.

**Pretreatment and Follow-up Evaluation.** Within 2 weeks of the start of treatment patients underwent a complete medical history and physical examination, assessment of vital signs, performance status and weight, 12-lead electrocardiography, neurological examination, chest X-ray, and CT or magnetic resonance imaging scan, brain CT or magnetic resonance imaging scan, liver CT scan or ultrasound, complete blood count, blood chemistry, and urine analysis. Blood counts were repeated weekly whereas blood chemistry, physical examination, assessment of performance status and weight, and chest X-ray were repeated before each course. Disease evaluations to assess response were carried out every other cycle using the same methods as baseline.

**Treatment.** Topotecan (SmithKline Beecham Pharmaceuticals) was supplied in vials containing 4 mg of the free base as lyophilized cake with no antibacterial preservatives. The lyophilized formulation was reconstituted with 4 ml of sterile water for injection before dilution with 5% Dextrose Solution (final dilution between 10 μg/ml and 500 μg/ml). Topotecan was administered as a 30-min i.v. infusion at the dose of 0.75 mg/$m^2$/day for 5

consecutive days. Cisplatin was administered i.v., on day 1, at the dose of 60 mg/m$^2$ over 15-60 min infusion along with adequate pre- and posthydration according to the local policy. Treatment cycles were repeated every 3 weeks if complete hematological recovery (ANC ≥1.5 x 10$^9$/liter, platelets ≥100 x 10$^9$/liter, and hemoglobin ≥9.0 g/dl) occurred, serum creatinine was ≤1.5 mg/dl, and drug related nonhemato-logical toxicity was resolved or was no longer clinically significant. In case of incomplete hematological or nonhematological recovery on day 22, treatment was delayed for a maximum of 2 weeks. Chemotherapy dose reductions were implemented when severe nadir toxicity was seen, which had recovered by the time of redosing. In case of nadir ANC <1.0 x 10$^9$/liter associated with fever or ANC <0.5 x 10$^9$/liter lasting ≥7 days, even in the absence of fever, or ANC nadir between 0.5-0.99 x 10$^9$/liter lasting beyond day 21, prophylactic granulated-colony stimulating factor was added with chemotherapy given at full dose. A topotecan dose reduction of 0.25 mg/m$^2$/day was required when the neutrophil toxicities occurred despite the prophylactic use of granulated-colony stimulating factor. Dose reduction was also mandatory if the nadir platelet count was <25 x 10$^9$/liter or in case of National Cancer Institute of Canada Clinical Trial Group grade III-IV nonhematological toxicity (except for nausea and alopecia). The dose of cisplatin was reduced to 40 mg/m$^2$ in case of creatinine clearance <60 ml/min and for peripheral neurotoxicity grade II. Treatment was discontinued if peripheral neurotoxicity greater than grade II was encountered. The dose of topotecan could be increased by 0.25 mg/m$^2$ if there was no toxicity greater than grade I during the previous course. The minimum and the maximum topotecan doses permissible were 0.5 mg/m$^2$ and 1.0 mg/m$^2$, and the minimum and maximum cisplatin doses allowed were 40 mg/m$^2$ and 60 mg/m$^2$.

**Table 1:** *Patient characteristics (eligible patients only)*

| | **No. (%) Sensitive (*n* = 68)** | **No. (%) Refractory (*n* = 42)** |
|---|---|---|
| **Sex** | | |
| Female | 14 (20.6) | 7 (16.7) |
| Male | 54 (79.4) | 35 (83.3) |
| **Age** | | |
| Median years (range) | 60 (38-73) | 55 (35-75) |
| **WHO PS** | | |
| 0 | 12 (17.6) | 5(11.9) |
| 1 | 48 (70.6) | 27 (64.3) |
| 2 | 8 (11.8) | 10 (23.8) |
| **Disease extent** | | |
| Limited | 18(26.5) | 14 (33.3) |
| Extensive | 50 (73.5) | 28 (66.7) |
| **Prior treatment** | | |
| Radiotherapy (RT) | 50 (73.5) | 17 (40.5) |
| Thoracic RT only | 27 | 7 |
| Brain RT only | 2 | 3 |
| Thoracic ± brain ± other RT | 20 | 6 |
| Other RT only | 1 | 1 |
| Chemotherapy (CT) | | |
| Median no. of drugs (range) | 3 (2-6) | 3 (2-4) |
| Median no. of courses (range) | 5 (3-10) | 5 (2-11) |
| Prior platinum CT regimen | | |
| No | 37 (54.4) | 25 (59.5) |
| Yes | 31 (45.6) | 17 (40.5) |
| Cisplatin-based regimen | 15 | 2 |
| Carboplatin-based regimen | 16 | 15 |
| Prior etoposide CT regimen | | |
| No | 7 (10.3) | 7 (16.7) |
| Yes | 61 (89.7) | 35 (83.3) |
| Median interval (in days) between end of first line treatment and progression | 165 | 30 |

Concomitant administration of antineoplastic agents, including drugs that have the potential to modulate the endocrine and/or immunological response to cancer, as well as investigational drugs, was not permitted. Prophylactic use of hematopoietic growth factors was not allowed during the first cycle. Palliative radiotherapy to nonindicator lesions was allowed.

Decisions regarding continuation of treatment were made on the basis of tumor reassessments every other cycle. A minimum of two courses had to be given before response evaluation; treatment was continued in case of

response or stable disease, at the discretion of the investigator, until progression or severe cumulative toxicity, or for a maximum of six courses.

**Table 2:** *Evaluation of activity (eligible patients)*

| | **No. (%) Sensitive (*n* = 68)** | **No. (%) Refractory (*n* = 42)** |
|---|---|---|
| CR[a] | 1 (1.5) | 0 (0.0) |
| PR | 19 (27.9) | 10 (23.8) |
| OR | 20 (29.4) | 10 (23.8) |
| (95% CI) | (19.0-41.7) | (12.1-39.4) |
| NC | 25 (36.8) | 11 (26.2) |
| PD | 4(5.9) | 16 (38.1) |
| Early death | | |
| Malignant disease | 1 (1.5) | 1 (2.4) |
| Toxicity[b] | 5 (7.4) | 0 (0.0) |
| Other | 3 (4.4) | 0 (0.0) |
| Not assessable | 10 (14.7) | 4(9.5) |

[a] CR, complete response; PR, partial response; OR, objective response; NC, no change; PD, progressive disease.
[b] One cardiac infarction, 1 renal failure with associated cardiac failure, 1 pulmonary embolism, 1 cardiorespiratory failure, and 1 neutropenic sepsis.

**Criteria for Evaluation of Response, Toxicity, and Survival.** Response and toxicity were evaluated according to WHO and NCIC CTG criteria, respectively (17). All of the responses had to be confirmed by two observations made not less than 4 weeks apart and were validated by a review committee including two independent expert radiologists. Overall survival was measured from the date of registration to the date of death regardless of the cause of death. Patients still alive at the time of analysis were censored at the last date known to be alive. Time to progression was measured from the date of registration to the date of documented progression or death. Patients without documented progression were censored at the date of death or last date known to be alive.

**Study Design and Statistical Considerations.** The study was designed as two distinct Phase II trials, one for the s group and the other for the r group. The primary aim of the study was to assess the antitumor activity and toxicity of topotecan combined with cisplatin in the two groups of patients. The secondary aim was to evaluate time to progression and overall survival.

Each study was designed according to the Simon's two-stage design (minimax; Ref. 18). In the r group, the objective was to select the treatment for additional study if the response rate was ≥30% and to reject if the response rate was ≤10%. In the s group, the objective was to select the treatment for additional study if the response rate was ≥50% and to reject if the response rate was ≤30%. In both studies, the type 1 and 2 errors were both set to 0.05. The overall survival time and the overall time to progression were estimated using the Kaplan-Meier technique (19).

## RESULTS

**Patient Demographics.** From January 1997 to April 1999 a total of 116 relapsed SCLC patients, 74 with s and 42 with r disease, were recruited from 24 institutions. In the s group, 6 patients were not eligible: 1 had no measurable lesions, 1 was registered after treatment start, 1 had a squamous cell histology, 1 had symptomatic brain metastases untreated with radiotherapy, 1 had a concurrent active infection, and 1 other had abnormal baseline blood tests. Therefore, 68 and 42 patients in the s and r group, respectively, were eligible. Ineligible patients were not included in the analysis. Main patient characteristics are presented in Table 1. In summary, most patients were males with a median age of 60 (s) and 55 (r) years, had a median performance status of 1, and had extensive disease. Brain metastases were present in 22% and 36% of patients with s and r disease, respectively. The majority of patients had received extensive prior treatment including radiotherapy (74% of s and 41% of r patients). The median number of drugs received during first-line chemotherapy was 3 with a median number of 5 treatment cycles for both s and r. Approximately 40% of patients had received prior platinum-based regimens in both the s and r group. Four patients were rechallenged, at first relapse, with the same first-line chemotherapy regimen before being treated with cisplatin-topotecan. The median duration between last first-line treatment day (including radiotherapy) and progression was 165 and 30 days for s and r patients, respectively.

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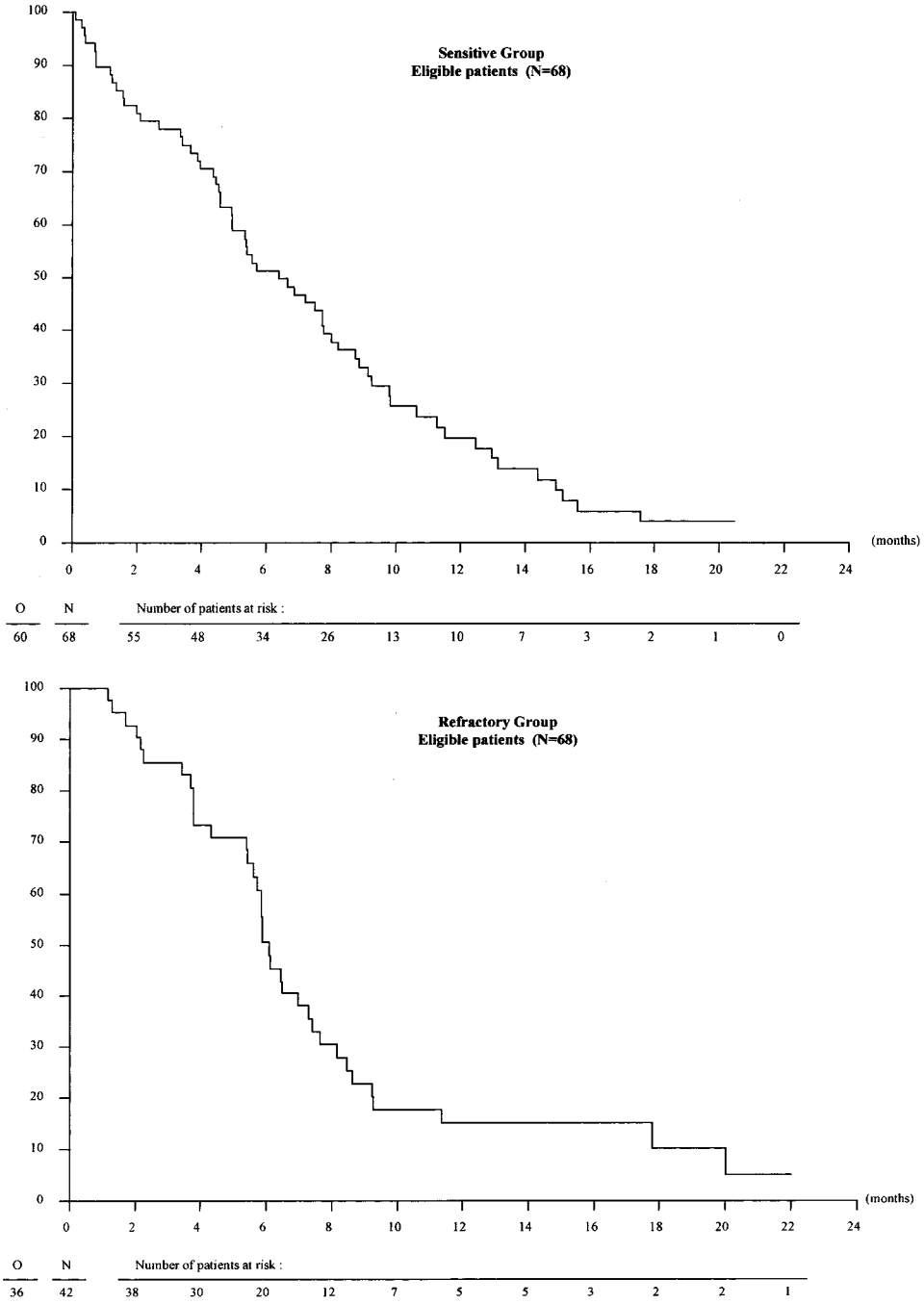
**Fig. 1**: *Actuarial survival according to prior treatment results. Refractory, actuarial survival of r patients (median survival = 6.1 months). Sensitive, actuarial survival of s patients (median survival = 6.7 months).*




**Response to Treatment.** A total of 398 courses (241 in s and 157 in r patients), with a median of 4 (range, 1-6) and 3 courses (range 0-10) per eligible patient, respectively, were administered. Of 110 eligible patients, 14 could not be assessed for response (10 s and 4 r patients). One never started treatment, 2 had inadequate radiological assessment, and 11 had received only 1 course of chemotherapy (4 for toxicity, 3 because of worsening general status, 3 because of intercurrent diseases, and 1 patient refused additional treatment). Of the other 96 patients (38 in the r and 58 in the s group, respectively), 10 patients died early before the first disease evaluation could be performed. Nine of these early deaths occurred in s patients. For 5 of these deaths relation to study drug was possible or could not be excluded (1 cardiac infarction, 1 renal failure with associated cardiac failure, 1 pulmonary embolism, 1 cardiorespiratory failure, and 1 neutropenic sepsis). Of the remaining 5 early deaths, 2 were judged as tumor-related, 2 were because of pulmonary embolism, and 1 because of a cerebrovascular accident. All of the early deaths were recorded as treatment failures. Nineteen partial responses (27.9%) and 1 complete response (1.5%) were obtained among s patients, whereas 10 partial responses (23.8%)

occurred among r patients. Overall response rate was 29.4% (95% CI, 19.0-41.7%) in s patients and 23.8% (95% CI, 12.1-39.4%) in r patients (Table 2). All but 3 of the responses were extramurally reviewed. There were 10 other cases (9 among s and 1 among r patients) with a documented ≥50% tumor size reduction, which did not qualify for partial responses because of the lack of response confirmation after a minimum of 4 weeks as required by the WHO response criteria.

Median survival of s patients was 6.4 months (95% CI, 5.0-8.0 months) and that of r patients was 6.1 months (95% CI, 5.6-7.7 months), with a 1-year survival rate of 19.7% (95% CI, 9.5-29.9%) and 15.2% (95% CI, 4.0-26.4%), respectively (Fig. 1). Median time to progression was 4.7 months (95% CI, 3.4-5.9 months) and 3.0 months (95% CI, 2.0-4.5 months), respectively.

**Toxicity.** The most frequent and severe toxicity was myelosuppression (Table 3). Leukopenia was almost universal, with severe (grade III-IV) neutropenia occurring in 3 of 4 of patients in both groups. At least one episode of febrile neutropenia occurred in 19% (s) and 15% (r) of patients, respectively, whereas presence of infection, regardless of neutrophil count, was recorded in a quarter of patients in both groups. One patient (s) died of neutropenic sepsis. Grade III-IV thrombocytopenia occurred in 74% and 63% in s and r patients, respectively, whereas hemorrhage grade I-III occurred in 21% (s) and 26% (r). Nonhematological toxicity was generally mild. Most frequent grade III-IV nonhematological toxicity (Table 4) consisted of nausea 3% (s) and 2% (r), vomiting 0% (s) and 10% (r), diarrhea 2% (s) and 2% (r), cardiovascular toxicity 12% (s) and 4% (r), and alopecia 19% (s) and 10% (r). The most common complaint was fatigue/malaise, which occurred in 52% (s) and 68% (r). Toxicity, especially myelosuppression, occurred most frequently during the first cycle of therapy, and required dose reductions in 41% (s) and 21% (r) or treatment delays in 62% (s) and 57% (r) of patients. Despite dose reduction at the second course, 20% (s) and 33% (r) of patients developed grade IV toxicity during the second course of therapy. Overall, 46.1% (s) and 36.9% (r) of cycles given, and 72.1% (s) and 66.7% patients required a dose reduction and/or delay because of toxicity. The median relative cisplatin and topotecan dose intensities were 86% and 84% in s patients, whereas they were 89% and 90%, respectively, in r patients.

**Table 3:** *Hematological toxicity (n = 109)*

| | **NCIC CTG grade** | |
|---|---|---|
| | **III (%)** | **IV (%)** |
| Leukopenia | | |
| Sensitive | 23 (33.8) | 32 (47.1) |
| Refractory | 18 (43.9) | 13 (31.7) |
| Neutropenia | | |
| Sensitive | 10 (14.7) | 42 (61.8) |
| Refractory | 11 (26.8) | 20 (48.8) |
| Thrombocytopenia | | |
| Sensitive | 13 (19.1) | 37 (54.4) |
| Refractory | 8 (19.5) | 18 (43.9) |
| Anaemia | | |
| Sensitive | 21 (30.9) | 4 (5.9) |
| Refractory | 13 (31.7) | 4 (9.8) |

## DISCUSSION

The results of this prospective Phase II study indicate that the combination of cisplatin and topotecan has activity in the treatment of relapsed SCLC and promising results in patients with refractory disease. In fact, in the r group, the response rate of 24% (95% CI, 12.1-39.4%) met the target level of activity (30%) required to consider the regimen worthy of additional testing. Surprisingly, however, we were unable to reach the target level of activity (50%) in patients with s disease. In fact, the response rate in this category of patients was only 29% (95% CI, 12%—39%). The 50% target response rate was set, based on the level of activity obtained in the same population of patients with single-agent topotecan. In fact, in a previous study performed in our group, topotecan yielded a 38% response rate (11), and in other similar studies response rate to single-agent topotecan in sensitive relapse SCLC ranged from 14% to 19% (13-15). Cisplatin is known to have a single-agent activity of 5-22% in relapsed patients (2) and to be synergistic with topotecan in preclinical models (20). With this background, a response rate of 50% was considered a suitable target level of activity, which would justify additional testing of this regimen in SCLC patients with sensitive relapse. However, considering the less optimistic topotecan and cisplatin single-agent Phase II results, a response rate of 30-40%, with the combination of these two agents, would probably be a more realistic target.

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**Table 4:** *Nonhematological toxicity (n = 109)*

| | NCIC CTG grade | | |
|---|---|---|---|
| | II (%) | III (%) | IV (%) |
| Allergy | | | |
| Sensitive | — (—) | — (—) | 1 (1) |
| Refractory | — (—) | — (—) | — (—) |
| Hypertension | | | |
| Sensitive | 1 (1) | 3 (4) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |
| Hypotension | | | |
| Sensitive | 5 (7) | 1(1) | — (—) |
| Refractory | 2 (5) | — (—) | — (—) |
| Other cardiovascular | | | |
| Sensitive | 3 (4) | 6 (9) | 2 (3) |
| Refractory | 2 (5) | 1 (2) | 1 (2) |
| Fever (abs. infect/+drug) | | | |
| Sensitive | 2 (3) | 1 (1) | — (—) |
| Refractory | 4 (10) | — (—) | — (—) |
| Arthralgia (joint pain) | | | |
| Sensitive | — (—) | — (—) | |
| Refractory | 2 (5) | — (—) | — (—) |
| Lethargy (fatigue/malaise) | | | |
| Sensitive | 16 (24) | 10 (15) | — (—) |
| Refractory | 8 (20) | 3 (7) | — (—) |
| Other flu-like symptoms | | | |
| Sensitive | 1 (1) | 1 (1) | — (—) |
| Refractory | 1 (2) | 1 (2) | — (—) |
| Anorexia | | | |
| Sensitive | 4 (6) | 3 (4) | 1 (1) |
| Refractory | 7 (17) | 1 (2) | — (—) |
| Diarrhea | | | |
| Sensitive | 3 (4) | 1 (1) | 1 (1) |
| Refractory | 8 (20) | 1 (2) | — (—) |
| Nausea | | | |
| Sensitive | 18 (26) | 2 (3) | — (—) |
| Refractory | 19 (46) | 1 (2) | — (—) |
| Vomiting | | | |
| Sensitive | 14 (21) | — (—) | — (—) |
| Refractory | 15 (37) | 4 (10) | — (—) |
| Pain/cramping | | | |
| Sensitive | 2 (3) | 3 (4) | — (—) |
| Refractory | 4 (10) | — (—) | — (—) |
| Stomatitis/oral | | | |
| Sensitive | 3 (4) | 1 (1) | — (—) |
| Refractory | 2 (5) | — (—) | — (—) |
| Other gastrointestinal | | | |
| Sensitive | 1 (1) | — (—) | 1 (1) |
| Refractory | — (—) | | |
| Dysuria | | | |
| Sensitive | — (—) | 1 (1) | — (—) |
| Refractory | — (—) | | |
| Other GU | | | |
| Sensitive | 2 (3) | — (—) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |

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**Table 4:** *Continued*

| | NCIC CTG grade | | |
|---|---|---|---|
| | **II (%)** | **III (%)** | **IV (%)** |
| Infection | | | |
| Sensitive | 8 (12) | 4 (6) | 3 (4) |
| Refractory | 7 (17) | 2 (5) | — (—) |
| Febrile neutropenia | | | |
| Sensitive | — (—) | 13 (19) | — (—) |
| Refractory | — (—) | 6 (15) | — (—) |
| Constipation | | | |
| Sensitive | 2 (3) | — (—) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |
| Headache | | | |
| Sensitive | 1 (1) | 2 (3) | — (—) |
| Refractory | 3 (7) | — (—) | — (—) |
| Motor neurotoxicity | | | |
| Sensitive | — (—) | 1 (1) | — (—) |
| Refractory | 3 (7) | — (—) | 1 (2) |
| Sensory neurotoxicity | | | |
| Sensitive | 1 (1) | 1 (1) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |
| Other neurological | | | |
| Sensitive | 4 (6) | 4 (6) | — (—) |
| Refractory | 2 (5) | 2 (5) | — (—) |
| Cough | | | |
| Sensitive | 12 (18) | 1 (1) | — (—) |
| Refractory | 10 (24) | 1 (2) | — (—) |
| Shortness of breath | | | |
| Sensitive | 17 (25) | 7(10) | — (—) |
| Refractory | 11 (27) | 3 (7) | 1 (2) |
| Other pulmonary | | | |
| Sensitive | 2 (3) | — (—) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |
| Alopecia | | | |
| Sensitive | 25 (37) | 13 (19) | — (—) |
| Refractory | 26 (63) | 4 (10) | — (—) |
| Other skin | | | |
| Sensitive | — (—) | 1 (1) | — (—) |
| Refractory | — (—) | — (—) | |
| Weight gain | | | |
| Sensitive | 1 (1) | — (—) | — (—) |
| Refractory | — (—) | — (—) | |
| Weight loss | | | |
| Sensitive | 2 (3) | — (—) | — (—) |
| Refractory | 1 (2) | — (—) | — (—) |
| Hemorrhage | | | |
| Sensitive | 5 (7) | 1 (1) | — (—) |
| Refractory | 1 (2) | 1 (2) | — (—) |
| Other toxicities | | | |
| Sensitive | 5 (7) | 3 (4) | 1 (1) |
| Refractory | 5 (12) | 1 (2) | — (—) |

More surprising perhaps, is the observation of a similar survival outcome in the two groups of patients (6.4 *versus* 6.1 months in s and r patients, respectively). This is in contrast with the results of the previous EORTC single-agent topotecan study where median survival in s and r patients was 6.9 and 4.7, respectively (11).

Several considerations can be examined to explain the lack of difference in outcome in the two groups of patients, and the unexpected discrepancy between a positive outcome in r disease and a negative one in s disease.

First, to distinguish between s and r patients, we used the 3-month response duration cutoff according to standard EORTC Lung Cancer Group criteria (11). However, in this trial the majority of patients in the s group had an interval from the end of first-line treatment to progression between 3 and 6 months. This relatively short response duration in the s group might have accounted for the small difference observed in the outcome between r and s patients in our study. Other groups have used different time-to-progression cutoff to distinguish between r and s relapse. The registration topotecan trial (15) used a 60-day cutoff, whereas other investigators have used a 6-month cutoff. We have recalculated response rates using these different criteria. Using a 60-days cutoff, response rate was 21% in s *versus* 20% in r patients. By using a 6-month cutoff, the response rate was 39% and 23%, respectively. However, it has to be noted that the number of patients with a time-to-progression >6 months in our study is too small to draw any meaningful conclusion.

Another aspect to be taken into consideration to explain the puzzling results of our study, is the type of prior first-line chemotherapy administered in this patient population. Forty-six percent (s) and 40% (r) of the patients had platinum-based first-line regimens; prior cisplatin was allowed only in case of response and if chemotherapy treatment had been completed at least 6 months before. This eligibility criteria was set to prevent cumulative cisplatin toxicity and to avoid cisplatin retreatment in patients resistant to this agent. Conversely, prior treatment with carboplatin was always allowed, in view of the lack of a complete cross-resistance and overlapping toxicity between the two platinum agents. This eligibility criteria may have selected out the poorest prognostic group, the cisplatin-resistant, from r patients thereby favoring the probability of response to a cisplatin-based chemotherapy in this category of patients as opposed to s patients where 22% of them had prior cisplatin and another 24% had prior carboplatin. In addition, almost all of the patients received etoposide-based chemotherapy, either platinum- or nonplatinum-based. Preclinical studies in cell lines indicate a possible collateral sensitivity, with increased tumor growth inhibition to topoisomerase-I inhibitors, such as topote-can, when cells have been pre-exposed to topoisomerase-II poisons, such as etoposide (21). This might partially explain the relative better outcome of patients with r, as compared with those with s disease, in our study.

Finally, it has to be noted that, because of severe myelo-suppression in the majority of patients during the first cycle of therapy, dosing was delayed frequently or reduced (53% of courses in the s group and 41% of courses in the r group), and the median number of administered courses was only 4 and 3 for s and r patients, respectively. In addition, 24 patients received only one course of therapy, either for occurrence of early (5 patients) or toxic (5 patients) death, or for other reasons such as early progression or worsening general status (5 patients), toxicity (5 patients), intercurrent diseases (3 patients), or refusal (1 patient). Nineteen of these 24 patients were in the s group. This high rate of s patients who received an inadequate amount of treatment might partially explain the low response rate observed in this group.

The schedule used in our study was designed empirically, based on preclinical data indicating synergy between topotecan and cisplatin, with cisplatin preceding topotecan administration (20) and on Phase I results (16). This schedule is associated with a high rate of myelosuppression, although in our study we did not observe a significant number of possible related complications, such as sepsis or bleeding, as reported in preliminary reports (22). However, more recent studies have shown that tolerability of the cisplatin-topotecan regimen can be improved, without compromising activity, by postponing the administration of cisplatin from day 1 to day 5 (23,24), which may prevent a negative pharmacological interaction between the two agents (23). In addition, an oral formulation of topotecan is in development, and preliminary clinical data seem to suggest similar activity with reduced toxicity, compared with the i.v. formulation (25). A combination of oral topotecan administered for 5 days combined with i.v. cisplatin on day 5 has been explored recently in patients with advanced non-SCLC, and appears active and devoid of a high rate of severe hematological toxicity (26). This latter regimen has been selected for additional development of the cisplatin-topotecan regimen in the first-line treatment of SCLC.

In addition to topotecan, other new agents have shown activity in the treatment of relapsed SCLC. Among these, paclitaxel has been the most extensively tested. A single-agent Dutch Phase II trial reported a 30% response rate in SCLC patients refractory to adriamycin-cyclophosphamide-etoposide chemotherapy (27). When the same group of investigators combined carboplatin with paclitaxel in patients with refractory SCLC, response rate reached 70% (28). However, the outstanding results of this study could not be confirmed by a more recent Greek trial of the same regimen in the same category of patients (29). CPT-11, another topoisomerase-I inhibitor, has also been studied extensively in relapsed SCLC (30). On the basis of positive results obtained in relapsed SCLC, this drug has been taken to first line in combination with cisplatin with some initial evidence of superiority when compared with a standard cisplatin-etoposide regimen (31). A similar first-line strategy is now being pursued

with the combination of cisplatin and topotecan.

In conclusion, the combination of i.v. cisplatin and topotecan, at the dose and schedule used in our study, shows activity in second-line treatment of SCLC, at least in patients with refractory disease, with reversible myelosuppression as the main side effect. The level of response rate observed in refractory patients is encouraging and warrants additional first-line testing of this regimen. The use of different schedules, such as the administration of cisplatin on day 5 along with the use of the oral formulation of topotecan, might be preferable to reduce myelotoxicity and improve feasibility in additional development of this combined regimen.

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